PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2005/001524	International filing date *(day/month/year)* 24.01.2005
Priority date *(day/month/year)* 23.01.2004	
International Patent Classification (IPC) or both national classification and IPC A61K9/16, A61K31/216, A61K31/155	
Applicant FOURNIER LABORATORIES IRELAND LIMITED	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21 and 22 (IA)

because:

☒ the said international application, or the said claims Nos. 21 and 22 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20,22-25
	No:	Claims	21
Inventive step (IS)	Yes:	Claims	1-20, 22-25
	No:	Claims	21
Industrial applicability (IA)	Yes:	Claims	1-20, 23-25
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 21 and 22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 99/40904 A (MERCK PATENT GMBH ;BONHOMME YVES (FR); BRIET PHILIPPE (FR)) 19 August 1999 (1999-08-19)
D2: US-A-6 074 670 (STAMM ANDRE ET AL) 13 June 2000 (2000-06-13)
D3: US-A-4 895 726 (CURTET BERNARD ET AL) 23 January 1990 (1990-01-23)
D4: DE SILVA S R ET AL: "Metformin and clofibrate in maturity onset diabetes mellitus: advantages of combined treatment" DIABETE & METABOLISME, MASSON, PARIS, FR, vol. 5, no. 3, 1 September 1979 (1979-09-01), pages 223-229, XP002083497 ISSN: 0338-1684
D5: EP-A-1 424 070 (FOURNIER LABORATORIES IRELAND LIMITED) 2 June 2004 (2004-06-02)

If not mentioned otherwise, the relevant passages are those mentioned in the International Search Report.

Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of claim 21 is not new.

D1 discloses a pharmaceutical composition comprising metformin and fenofibrate or bezafibrate. Therefore, the subject-matter of claim 21 of the present application is not new in the light of D1.

The subject-matter of present claim 1 appears to be new in the light of the prior art. Prior art does not disclose a pharmaceutical composition comprising

(a) particles of metformin and particles of a fibrate
(b) in a combined amount of at least 50% by weight, based on the total weight of the composition
(c) wherein the weight ratio of metformin to fibrate is between 500:90 and 850:35.

Art 33(3) D1, which is considered to represent the most relevant state of the art, discloses the a granulate comprising metformin and fenofibrate and discloses the synergism of the two active ingredients.
The problem to be solved by the present invention may therefore be regarded as how to provide an imroved medicament comprising a fibrate and metformin.

The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claim 21 does not involve an inventive step in the sense of Article 33(3) PCT.
Present claim 21 suggests to solve the problem posed by providing a pharmaceutical composition comprising metformin and fenofibrate. This has been anticipated by the prior art.

D2 discloses granulates comprising micronized fenofibrate having a dissolution profile of fenofibrate which is inferior to that of the present application.
D3 discloses granulates comprising fenofibrate that is co-micronized with

sodium laurylsulfate.
D4 discloses the pharmacological synergism between another fibrate (clofibrate) and metformin
In summary, prior art discloses pharmaceutical compositions comprising fibrates that are co-micronized with surfactant to achieve a particle size below 10 micrometers from which the present subject-matter differs in that the present composition comprises an combined amount of metformin and fibrate of at least 50% by weight and wherein the weight ratio of metformin to fibrate is between 500:90 and 850:35.

The present application provides reasonable *in vitro* data that addition of metformin in an amount and weight ratio as defined by present claim 1 to a composition comprising a fibrate results in an improved dissolution profile of the fibrate. This could not have been derived from the prior art.
It is therefore noted that present claims 1-20 and 22-25 are considered as being inventive in the sense of Article 33(3) PCT.

Art 33(4) For the assessment of the present claims 21 and 22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The subject-matter of claims 1-20 and 23-25 is considered to be industrially applicable in the sense of Art 33(4) PCT.

Re Item VI

Certain documents cited

D5 discloses pharmaceutical compositions comprising metformin and fenofibrate.